

Remarks

Prior to this amendment, claims 1-28, 34-39, 44-51 and 53-83 are pending. Claims 1-4, 6-9, 11, 16, 17, 19, 25, 26, 76, and 81 are amended herein. Claims 84-87 are added. No additional claims are canceled. After entry of this amendment, **claims 1-28, 34-39, 44-51 and 53-88 are pending in this application.**

Support for amended claim 1 can be found throughout the specification, for example at page 8, lines 14-15. Support for amended claim 2 can be found in the specification, for example, at page 10, lines 4-6. Support for amended claims 3 and 17 can be found in the specification at page 10, lines 11-13. Support for the amendment of claims 16, 25 and 26 can be found in the specification at page 9, line 19. Support for new claims 84 and 85 can be found in the specification at page 8, lines 14-28. Support for new claims 86 and 87 can be found in the specification at page 10, lines 4-6.

Claims 4, 6-9, 11, 76 and 81 are amended to correct matters of form. Claim 19 is amended to correct dependency.

No new matter has been added by these amendments. Unless specifically stated otherwise, none of these amendments are intended to limit the scope of any claim.

Acknowledgement of Priority Claim

Applicants thank the Examiner for acknowledging that the application claims the benefit of U.S Provisional Application No. 60/120,288, filed February 16, 1999.

Telephone Interview

Applicants thank Examiner Minnifield for the courtesy of the April 21, 2004, telephone interview with their representatives Dr. Tanya Harding and Dr. Anne Carlson. During the interview, the rejection of the claims under 35 U.S.C §112, second paragraph, was discussed briefly. On the basis of a draft set of amended claims faxed to Examiner Minnifield, the Examiner indicated that the amendments to the claims satisfactorily address the 35 U.S.C §112 rejections. The Examiner also noted that the term "Nonidet®P40" should include its generic description. In addition, the rejection of the claims under 35 U.S.C §102 (b) and (e) were discussed.

Finally, it was determined that the Examiner was looking at a scanned copy of the specification that appears to be missing a few letters (particularly the letter "O"). It was agreed that Applicants would

review the scanned version of the specification (as available on the USPTO online Patent Application Information Retrieval database, PAIR) and all typographical errors due to missing letters would be corrected.

Although express and complete agreement was not reached on all of the issues discussed, it is believed that this response is in accordance with that discussion and suggestions made by the Examiner.

Correction of Informalities in the Specification

The Examiner has objected to the specification because allegedly letters are missing from words in various places in the specification. As agreed in the telephone interview, Applicants have amended the specification to add the "O" missing from various locations in the scanned version at the Office. In addition, Applicants have amended the specification to correct other minor typographical errors. Applicants respectfully request that the objection to the specification be withdrawn.

Rejections Under 35 U.S.C. §112 second paragraph

Claims 2, 4-11, 16, 19, 25-28, 47, 76, and 81 are rejected under 35 U.S.C. §112 second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Individual rejections of these claims are discussed individually below.

"small volume"

Claims 2 and 16 are rejected as indefinite because the recitation of "small volume" is allegedly vague. Applicants traverse this rejection. However, in the interest of advancing prosecution, Applicants have amended claims 2 and 16 to recite "solubilizing the extracted cell contents in less than about 20 µl of a buffer . . ." Applicants respectfully request that this rejection of claims 2 and 16 be withdrawn, since the language that the Examiner believes is indefinite has been removed.

"the protein sample"

Claims 4-11 are rejected as allegedly indefinite because the claims lack positive antecedent basis in the recitation of "the protein sample." Applicants have amended claims 4, 6, 8, 9, and 11 to refer to "the isolated protein sample." Applicants respectfully request that this rejection of claims 4-11 be withdrawn in light of these amendments.

“abbreviations”

Claims 16 and 25-28 are rejected as allegedly indefinite because the claims contain abbreviations that have not been defined. Applicants have amended claims 16, 25, and 26 to refer to the chemical name of the recited compound. Claims 27 and 28 depend from claim 26 and thereby incorporate the amendments. Applicants respectfully request that this rejection of claims 16 and 25-28 be withdrawn in light of these amendments.

“immunoassay”

Claim 19 is rejected as allegedly indefinite because the claim lacks positive antecedent basis in the recitation of “immunoassay.” Applicants have amended claim 19 to depend from claim 18, which provides antecedent basis. Thus, Applicants respectfully request that this rejection be withdrawn.

“calibrating”

Claim 47 is rejected as allegedly indefinite because the claim lacks positive antecedent basis in the recitation of “calibrating.” Applicants traverse this rejection.

Applicants have amended claim 6 (from which claim 47 depends) to recite “calibrating the assay to indicate the amount of protein of interest present in the isolated protein sample.” Thus, claim 47 finds proper antecedent basis for “calibrating.” Applicants respectfully request that the rejection of claim 47 be withdrawn since the claim, as amended, is not indefinite.

“which is used as to calibrate”

Claims 76 and 81 are rejected as allegedly being indefinite because the recitation of “which is used as to calibrate” is vague. Applicants traverse this rejection.

In the interest of advancing prosecution, Applicants have amended claims 76 and 81 to recite “wherein each of the two or more purified proteins is used to calibrate.” Applicants respectfully request that the rejection of claims 76 and 81 be withdrawn since the claim, as amended, is not indefinite.

Rejections Under 35 U.S.C. §102(e)

Bonner et al. (U.S. Patent Number 6,251,516; issued June 26, 2001)

Claims 1-28, 34-39, 44-51 and 53-83 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Bonner et al. (U.S. Patent Number 6,251,516; issued June 26, 2001). Applicants traverse this rejection.

As suggested by the Examiner, Applicants submit herewith a Declaration under 37 C.F.R. 1.132 (the Declaration) from Lance A. Liotta and Michael R. Emmert-Buck, the only two overlapping co-inventors of both Bonner et al. and of the subject patent application. The Declaration (at paragraph 4) states that the concept of analyzing proteins from a population of microdissected cells is the work of co-inventors Liotta and Emmert-Buck to the extent that this concept is disclosed, but not claimed, in Bonner et al. Thus, Applicants submit that the Declaration overcomes the rejection based on Bonner et al. because the disclosure is not “by another.”

In addition, Applicants submit that the specific methods of analyzing *proteins that are extracted, or isolated*, from microdissected cells are *neither disclosed, nor claimed* in Bonner et al. Bonner et al. describes that proteins can be *analyzed in microdissected cells*. For example, in Bonner et al. zymography was used to measure enzyme (cathepsin B) activity. No teaching is provided in Bonner et al. that would enable one of ordinary skill in the art to first *extract* the protein component of microdissected cells in order to obtain further information about the protein component, such as protein concentration, the phosphorylated state of proteins, or the presence of novel proteins in a microdissected sample.

In contrast, the pending claims recite methods of analyzing the protein content of cells extracted by laser capture microdissection, by first *isolating a protein sample* from the cells. One of skill in the art would not have known from the disclosure in Bonner et al. that proteins could be extracted from microdissected cells and the prior art did not teach how to extract and isolate the protein component of such a small sample of cells.

Thus, the currently claimed methods of extracting or isolating a protein sample from microdissected cells, prior to analyzing the protein sample, are distinct from the subject matter disclosed in Bonner et al. Applicants submit that the Declaration, alone or in combination with the above arguments, overcomes the rejection and respectfully request that the rejection be withdrawn.

Olsen et al. (*Neuroendocrinology*, 50/4:392-399, 1989)

Claims 1-3, 8, 12, 13, 15-17 and 23-28 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Olsen et al. (*Neuroendocrinology*, 50/4:392-399, 1989). Applicants traverse this rejection.

Applicants respectfully disagree with the Examiner's assertion that the methods of analyzing protein tissue samples disclosed in Olsen et al. anticipate the claimed invention. Olsen et al. discloses the use of the "punch biopsy" method for obtaining tissue samples, where 0.5, 0.75, or 1.0 mm punches are collected (Olsen et al., at page 393, left column, second paragraph). The punch biopsy method is performed without the aid of a microscope and the biopsies are obtained randomly within different regions of the brain, such as the ventromedial hypothalamus. However, without the use of a microscope in the punch biopsy method, specific cell types within the brain regions cannot be specifically identified and then isolated. Moreover, the diameter of the smallest punches (0.5 mm) disclosed in Olsen et al. are at least approximately 10-fold larger than the areas microdissected by the Applicants' method. For example, the specification at page 13, lines 20-23, indicates that the laser beam used to obtain the cells is in the range between 5 and 60 μm . In addition, the specification at page 8, lines 10-12 indicates that Applicants method requires high power microscopic visualization. Thus, Applicants' method of analyzing the protein content of a population of cells uses *microscopic visualization* combined with *micron-size diameter biopsies* in order to obtain a specific cell population from a heterogeneous tissue sample. There is no teaching in Olsen et al. to identify and isolate populations of specific cell types using 1) micron-diameter biopsies and 2) microscopic visualization.

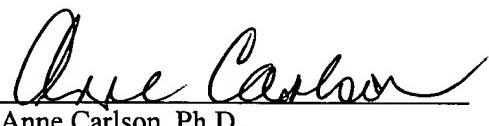
In the interest of advancing prosecution, Applicants have amended claim 1 to recite "extracting the population of cells from the tissue sample using microdissection under microscopic visualization." This is clearly distinguishable from the teaching of Olsen et al. Claims 2, 3, 8, 12, 13, 15-17 and 23-28 depend from claim 1 and therefore incorporate the amendment. Thus, Applicants respectfully request that this rejection of claims 1-3, 8, 12, 13, 15-17 and 23-28 be withdrawn.

CONCLUSIONS

Based on the foregoing amendments and arguments, the claims are in condition for allowance and notification to this effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of the claims, please telephone the undersigned at (503) 226-7391.

Respectfully submitted,

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